REMARKS

Claim 14 has been amended, and claims 17-18, 29, and 31-32 have been cancelled herein. Claims 14, 19-28, 30, and 33-44 are pending and currently under consideration.

Claim 14 has been amended to recite: "A delivery mixture comprising a delivery agent consisting of a generation 2 to 5 dendrimer ~~and~~ mixed with a nucleic acid capable of mediating RNA interference (RNAi)." Support for the amendment lies in the specification as filed, for example, at paragraph [0075], [102], [103], and [111] of the numbered paragraphs of the Patent Application Publication of the specification as filed. No new matter is added by virtue of the amendments. Entry and consideration of the amendments and remarks contained herein is requested.

INTERVIEW SUMMARY

Applicant appreciates the Examiner's time and consideration during a telephone interview conducted October 16, 2007. During the interview, the Examiner and the undersigned discussed the remaining rejection under 35 USC § 112, first paragraph, the rejection under 35 USC § 102(e), and the rejections under 35 USC § 103(a) in particular with reference to the Yoo et al. reference and the prior art considered as a whole. Additionally, the withdrawal of the rejections of claim 39 under 35 USC 103(a) regarding dendrimer 4 was discussed for clarification.

REJECTIONS UNDER 35 USC § 112

Rejections under 35 USC § 112, first paragraph

Claims 14 and 17-44 were rejected under 35 USC §112, first paragraph, as failing to comply with the written description requirement. The Office Action maintains that the recitation of "comprising a generation 2 to 5 dendrimer" in the claims lacks written description as not providing support for a generation 4 dendrimer. Applicant respectfully traverses the rejection.

As discussed in Applicant's prior submissions, Examples 1, 2, and 7 (at paragraphs 0102, 0103, and 0111) utilize a generation 4 dendrimer in experiments to demonstrate utility and efficacy of Applicant's invention. The Declaration of Tariq M. Rana under 37 CFR §1.132 (Rana Declaration) filed with the Response submitted 11/07/2006 supports the fact that the experiments described in the application as filed were carried out using a generation 4 dendrimer. See Rana Declaration at paragraphs 2-4 and 6-8, and particularly at paragraph 8 in the method description "Cellular Uptake of siRNA by Nanoparticles." Support in the Figures and Examples was included in the application as filed, as well as in the priority document, Provisional Application No. 60/430,520 filed 11/26/2002 (hereinafter, "the Priority Application"). See Rana Declaration at paragraph 3. Applicants therefore submit that the instant

claims should be accorded a priority date of 11/26/2002. Thus, Applicant submits support for each of generation 2, generation 3, generation 4, and generation 5 dendrimers lies in the specification as filed and in the priority document as filed. As such, no new matter is added by virtue of the recitation of "comprising a generation 2 to 5 dendrimer." Applicant respectfully requests reconsideration and withdrawal of the rejection. Furthermore, Applicant respectfully requests that the 11/26/2002 effective filing date of the Priority Application be accorded to the instant claims.

In the telephone interview conducted October 16, 2007, support for generation 4 dendrimer in the application as filed (as well as the Priority Application) was discussed. The Examiner indicated during the discussion that submission of an additional declaration with copies of notebook pages evidencing use of a generation 4 dendrimer in the experiments would be sufficient evidence to support such a showing.

Applicant submits herewith the SECOND DECLARATION OF TARIQ M. RANA UNDER 37 C.F.R. §1.132 (hereinafter Rana Declaration 2) and attached Exhibits further in support of the fact that the experiments described in the application as filed (and the Priority Application as filed) were carried out using a generation 4 dendrimer. Exhibits 1-11 are experiments and results which correspond to experiments carried out and described in the application as filed, as well as in the priority document provisional application as filed 11/26/2002 (Priority Application). See Rana Declaration 2 at paragraphs 2-10. Exhibits 2 and 5 evidence the use of generation 4 PAMAM dendrimer in experiments. See Rana Declaration 2 at paragraphs 5b and 5e and paragraph 6. Each of the experiments in Exhibits 1-11 used generation 4 PAMAM dendrimer. See Rana Declaration 2 at paragraph 6. Exhibits 1-11 are experiments and results corresponding to Example 1 (paragraph [0102] of the published application and FIGS. 1A and 1B), Example 2 (paragraph [0103] of the published application and FIG. 2), and Example 7 (paragraph [0111] of the published application and FIGS. 9A –9I) of the instant application. See Rana Declaration 2 at paragraph 7. Exhibits 1-11 are experiments and results corresponding to Example 2 (page 19 line 23 to page 20, line 31 and FIGS. 1A and 1B), Example 3 (page 21, lines 1-21 and FIG. 2), and Example 8 (page 24, line 29 to page 25, line 14 and FIGS. 9A –9I) of U.S. provisional patent application no. 60/430,520. See Rana Declaration 2 at paragraph 8. The experiments described in the '176 application and in U.S. provisional patent application no. 60/430,520 used a generation 4 PAMAM dendrimer as a delivery agent mixed with a nucleic acid capable of mediating RNA interference. See Rana Declaration 2 at paragraphs 9 and 10.

Applicant thus submits that the recitation "comprising a generation 2 to generation 5 dendrimer" is fully supported in the specification as filed, as generation 2, 3, and 5 dendrimers are depicted in the Figures and specification, and generation 4 dendrimers were utilized in Experiments 1, 2, and 7 of the

specification as filed. Reconsideration and withdrawal of the rejection under 35 USC §112, first paragraph is respectfully requested.

REJECTIONS UNDER 35 USC §102

Claims 14, 20, 22-24, and 43 remain rejected under 35 USC §102(e) as being anticipated by Frechet et al. (U.S. Patent No. 7,097,856) ("Frechet"). Applicant respectfully traverses the rejection.

The Office Action maintains Frechet teaches a delivery mixture comprising a dendrimer and a nucleic acid, which, when broadly interpreted, would encompass a dendrimer conjugated with a nucleic acid molecule. Applicant reiterates traversal of the rejection. The disclosure of Frechet does not anticipate Applicant's presently claimed invention because Frechet teaches a delivery compound consisting of a dendrimer conjugated to a desired agent to be delivered.

During the telephone interview October 16, 2007, the difference between a delivery mixture as claimed in the present application, and the conjugate molecule described in Frechet was discussed. The Examiner indicated that a conjugate molecule described in Frechet in a buffer would constitute a mixture of a molecule and buffer, and thus maintains that the disclosure of Frechet reads on the claimed invention. Applicant appreciates the Examiner's acknowledgement during the discussion that if the claims recited a mixture of two separate molecules, this would distinguish over Frechet. Applicant respectfully maintains traversal of the maintained rejection and asserts the present invention provides a mixture of a dendrimer molecule and a nucleic acid molecule (i.e., mixture of two separate molecules), which is neither disclosed nor suggested by Frechet. Further, Applicant maintains that one skilled in the art would recognize that the claims provide for a mixture of separate molecules, when the claims are interpreted in view of the specification.

However, in an effort to advance prosecution and address the concerns of the Examiner, Claim 14 has been amended to recite: "A delivery mixture comprising a delivery agent consisting of a generation 2 to 5 dendrimer mixed with a nucleic acid capable of mediating RNA interference (RNAi)." Support for this amendment lies in the specification as filed (as well as in the Priority Application as filed), for example at paragraphs [0074]-[0075] of the published specification (section "siRNAs Mixed with Delivery Agents"). It is believed the present amendments address any outstanding concerns stated in the Office Action. Reconsideration and withdrawal of the rejection under 35 USC §102 is respectfully requested.

REJECTIONS UNDER 35 USC §103

Rejection under 35 USC § 103(a) over Woolf, Olejnik et al., Grigoriev et al., and Yoo et al.

Claims 14, 19-20, 23-34, 38-42 and 44 remain rejected under 35 USC §103(a) as being unpatentable over Woolf, Olejnik et al., Grigoriev et al., and Yoo et al.

Applicant appreciates the Examiner's acknowledgment of lack of obviousness of use of a generation 4 dendrimer in view of the teaching of Yoo et al.

The Office Action asserts: "given that Yoo et al. outlines the ideal characteristics for a delivery vehicle comprising a nucleic acid and demonstrates dendrimers are effective at delivery [of] nucleic acids to cells and further states that dendrimers are useful for therapeutic applications, it would have been obvious to use a dendrimer, *particularly a generation 5 dendrimer as instantly claimed*, as a delivery vehicle for nucleic acids." See Office Action mailed 7/26/07 at page 6, top paragraph (emphasis added). The Office Action further states: "because Yoo et al. demonstrate the general conditions necessary for assessing the activity of a dendrimer – nucleic acid mixture and further demonstrate the routine nature of testing various ratios of dendrimer to oligonucleotide, from 15μg/ml to 90μg/ml (see Figure 1 and Figure 2) for optimization of the most efficient ratio for delivery and gene inhibition, these conditions would not be considered beyond the level of routine optimization." See Office Action at page 6, lower paragraph through top of page 7. Applicant respectfully disagrees with the conclusions stated in the Office Action and reiterates traversal of the rejection maintained under 35 USC §103.

First, Applicant respectfully disagrees with the Examiner's characterization that the teaching of Yoo et al. provides a teaching sufficient such that use of a generation 5 dendrimer as a delivery agent mixed with a nucleic acid capable of mediating RNA interference would be obvious. This assertion of obviousness relies on a finding that one of ordinary skill in the art would have selected a generation 5 dendrimer as a preferred delivery agent for modification of a delivery mixture for delivery of alternative nucleic acids. Based on the art as a whole, however, Applicant submits a person skilled in the art would not have selected a generation 5 dendrimer as a preferred delivery agent.

Close examination of the experiments, discussion and results of Yoo et al. teach that dendrimers demonstrate moderate activity for delivery of antisense oligonucleotide, which is diminished as lower generation dendrimer mixtures are utilized. For example, a generation 7 dendrimer confers moderate delivery activity as compared to industry standards, which is diminished upon use of generation 5 dendrimer; and a generation 4 dendrimer does not confer delivery activity. Further, when compared to transfection reagents known in the art to successfully deliver oligonucleotide, generation 7, 5 or 4 dendrimers demonstrated low activity or no activity. For example, Superfect™ (QIAGEN, Valencia, CA), a proprietary but commercially available highly branched activated dendrimer useful for nucleic acid transfection, confers a high level of activity in serum free medium; and the activity conferred using LIPOFECTAMINE™ (Invitrogen Corp., Carlsbad, CA), a cationic lipid based transfection agent used as a standard in the art, is even more improved over the effects demonstrated by Superfect. See Yoo et al.,

Figure 2, Figure 3, and at page 1801, first column. Thus, as the level of dendrimer generation or size of cationic agent is increased, the transfection activity of the agent also increased. In view of the results described in Yoo et al., even assuming one skilled in the art would be motivated to select a dendrimer disclosed by Yoo et al. for a delivery agent and modification to arrive at a delivery mixture comprising a delivery agent consisting of a dendrimer mixed with a nucleic acid capable of mediating RNAi, one would certainly not be motivated to select a generation 5 dendrimer because Yoo et al. teach a generation 5 dendrimer is not optimal. Rather, one would be motivated to select a larger dendrimer (e.g., a generation 7 dendrimer or even a larger generation dendrimer) as a preferred delivery agent, and not a generation 5 dendrimer as presumed in the Office Action.

Furthermore, additional results in the art support the position that one skilled in the art would have no motivation to select a generation 5 dendrimer as a preferred delivery agent for modification. "A *prima facie* case of obviousness may [also] be rebutted by showing that the art, in any material respect, teaches away from the claimed invention." *In re Geisler*, 116 F.3d 1465, 1471 (Fed. Cir. 1997). For example, Bielinska et al. (Nucleic Acids Research, 1996, Vol 24, No. 11, pp. 2176-2182., cited in the Office Action dated 8/23/05 in the rejection under 35 USC §102), like Yoo et al., teaches that dendrimers can be used as a transfection agent for delivery of antisense oligonucleotides and plasmid expression vectors coding antisense mRNA. See Bielinska et al. When various generations of dendrimers were assessed for optimal carriers for in vivo delivery of antisense oligonucleotides, generation 10 and generation 7 dendrimers were more effective than a generation 6 dendrimer in conferring delivery of antisense, as measured by inhibition of luciferase expression. See Bielinska at page 2178, last paragraph through page 2179 and Figure 4. Furthermore, when generation 5 and generation 7 dendrimers were assessed for transient transfection of Rat2Luc#4A7-4 cells and inhibition of constitutive luciferase expression was measured, only a generation 7 dendrimer conferred delivery resulting in approximately 40% inhibition of luciferase expression. A generation 5 dendrimer, which had previously been found ineffective in transfecting Rat2 cells, did not alter luciferase expression. See Bielinska et al., at page 2180, last paragraph and Figure 8. The teaching of Bielinska et al. amounts to a teaching away of the use of a generation 5 dendrimer as a preferred delivery agent. Thus, even assuming one skilled in the art would select a dendrimer as a preferred delivery agent for modification and production of a delivery mixture, one skilled in the art would be motivated to select a dendrimer that is higher than a generation 5 dendrimer in view of the results in the art as a whole.

Second, the assertion of obviousness in the Office Action maintains only routine testing of ratio of dendrimer to oligonucleotide is required for optimization of working conditions to produce an effective delivery mixture of nucleic acids. Based on the teaching of Yoo et al., however, a person skilled in the art would require more than routine optimization to arrive at a delivery mixture as presently claimed.

In addition to the correlation of improved delivery effect with higher generation dendrimer, Yoo et al. instructs that effective delivery and activity is dependent upon concentration of oligonucleotide, charge ratio of oligonucleotide to dendrimer, and generation of dendrimer used. See Yoo et al., at Figures 2-5 and 7, and page 1801, left column, first full paragraph, through second column, first paragraph, and at page 1803, entire Discussion. Further, the presence of increasing amounts of serum negatively influences the activity of the complexes even in the presence of different generation dendrimer complex, or optimized concentration, and charge ratio. See e.g., Yoo et al., Figures 1-7. Thus, in assessing activity of delivery complexes, numerous factors -- including dendrimer generation, oligonucleotide concentration, charge ratio, and presence of serum -- are factors that require optimization. The number of optimization factors is more than routine testing of various ratios of dendrimer to oligonucleotide as maintained in the Office Action. Modification of multiple factors (each factor comprising multiple possibilities of changes in conditions) results in combinations amounting to a large number of possibilities capable of being explored. Such a task entails exploration of numerous possibilities that extends beyond routine experimentation and optimization. Due to the large number of possible conditions, one skilled in the art would not have a reasonable expectation as to what ranges of each parameters would be successful in providing a delivery mixture comprising a delivery agent consisting of a generation 2 to 5 dendrimer mixed with a nucleic acid capable of mediating RNA interference (RNAi).

Thus, the teaching of Yoo et al. does not provide guidance or direction such that a generation 5 dendrimer would be selected by the ordinary skilled artisan as a preferred delivery agent for modification of a delivery mixture. Furthermore, when the prior art is considered as a whole, including the teachings of Bielinska et al., a generation 5 dendrimer would certainly not be selected as a preferred delivery agent because the art teaches a) generation 5 dendrimer is not the optimal generation dendrimer for use, and b) lack of activity of a generation 5 dendrimer teaches away from use as a delivery agent. Additionally, numerous optimization parameters necessary for modification of a delivery mixture as taught by Yoo et al. amounts to optimizing conditions such that one skilled in the art would not have a reasonable expectation of success in providing a delivery mixture according to the presently claimed invention using only routine experimentation.

As discussed in Applicant's prior response, the teaching of Woolf relating to use of a dendrimer in connection with dsRNA molecules amounts to nothing more than an invitation to experiment. The single mention of PAMAM dendrimers at paragraph 203 as merely one possible example of numerous potential delivery agents provides no guidance of any parameters for appropriate conditions, nor any suggestion of which, if any, of the lengthy list of delivery agents would be suitable to confer effective delivery. At best, the teaching of Woolf amounts merely to an obvious to try situation, with no guidance such that one skilled in the art would have had any reasonable expectation of success. Thus, whether

taken alone or in combination with Yoo et al., the teaching of Woolf does not remedy the deficiency of Yoo et al.

As acknowledged in Applicant's prior responses, Olejnik discloses the design, synthesis, and evaluation of a non-nucleosidic photocleavable biotin phosphoramidite (PCB-phosphoramidite) for simple purification and phosphorylation of oligonucleotides; and Grigoriev discloses use of psoralen-oligonucleotide conjugates useful for triple helix formation and cross-linking to DNA following UV irradiation. None of Olejnik et al. or Grigoriev et al., whether alone or in any combination with Woolf and/or Yoo et al., provide any teaching to lead one skilled in the art to produce a delivery mixture comprising a delivery agent consisting of a generation 2 to 5 dendrimer mixed with a nucleic acid capable of mediating RNA interference. Nor would one skilled in the art expect that such a composition would successfully deliver a nucleic acid capable of mediating RNA interference. Thus, neither Olejnik et al. or Grigoriev et al. remedy the deficiencies of Woolf and/or Yoo et al., whether alone or in any combination with Woolf and Yoo et al. Reconsideration and withdrawal of the rejection under 35 USC §103(a) is respectfully requested.

Secondary Considerations

Whether an art is predictable or whether the proposed modification or combination of the prior art has a reasonable expectation of success is determined at the time the invention was made. See MPEP, 2143.02, citing *Ex parte Erlich*, 3 USPQ2d 1011 (Bd. Pat. App. & Inter. 1986). Furthermore, failure of others is a secondary consideration or indicia of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18. As discussed in Applicant's prior response, attempts to substitute siRNA for antisense oligonucleotides as suggested by the Examiner have demonstrated that *success was certainly not predictable, expected or obvious*. In support of Applicant's argument, Kang et al. was submitted and discussed. See Amendments and Responses dated 11/07/06 and 05/03/07, and Kang, H., et al., *Pharm Res*. 22:2099-2106 (2005).

Whether or not applicant agrees with the Examiner that Kang demonstrates formation of strong dendrimer-oligonucleotide complex formation, or that Kang demonstrates similar cellular distribution of siRNA and antisense which is delivered to cells -- formation of complexes and/or minimal delivery and distribution in cells *alone* does not equate with or guarantee sufficient delivery of oligonucleotide for successful activity within a cell. Thus, while the Examiner characterizes the results of Kang as evidence that one would expect an siRNA molecule to behave *identical* to an antisense molecule in dendrimer-nucleotide mixtures since the molecules "are both nucleic acids that encounter the same delivery problems" (see Office Action dated 01/03/07 at page 15), the conclusions and reported results of Kang are *directly contrary to this interpretation*. In fact, Kang's interpretation of the data and conclusion is that

"gene expression was partially inhibited by the antisense-BPT complex and weakly inhibited by the siRNA-BPT complex when both were tested at nontoxic levels of dendrimer...Dendrimer-oligonucleotide complexes were moderately effective for delivery of antisense and only poorly effective for delivery of siRNA". See Kang at page 2099, Abstract at Results.

In the present Office Action, the Examiner maintains that the results of Kang et al. should not be interpreted as a failure of success of delivery of a siRNA complexed with a dendrimer. Applicant respectfully points out that the teaching of Kang et al. amounts to a lack of demonstration of a reasonable expectation of success in achieving predictable results in view of the art. Because, as stated in the prior Office Action, and restated in the present Office Action at page 8, lower paragraph: "one would expect to be able to produce a delivery mixture comprising a dendrimer mixed with a nucleic acid capable of mediating RNAi given they are both comprised of nucleic acids." Furthermore, as discussed in the Office Action and acknowledged in Applicant's prior response and above, Kang demonstrates formation of strong dendrimer-oligonucleotide complex formation, and Kang demonstrates similar cellular distribution of siRNA and antisense which is delivered to cells. Thus, if a delivery mixture comprising an siRNA compound is obvious, one would expect similar predictable results with an siRNA compound as an antisense compound. Such expectation was also asserted by the Examiner in the prior Office Action: "one would expect an siRNA molecule to behave identical to an antisense molecule in dendrimer-nucleotide mixtures since the molecules 'are both nucleic acids that encounter the same delivery problems'" (see Office Action dated 01/03/07 at page 15). Thus, the failure of success asserted by Kang et al. is not necessarily a complete failure to deliver any nucleic acid to a cell. Rather the failure of Kang is a lack of demonstration of a reasonable expectation of predictable or successful results.

Applicant reiterates the lack of success by Kang et al. is more than mere failure of another of skill in the art to carry out combined teachings in the prior art. As previously noted, experiments carried out in Yoo et al. and Kang et al. were in fact done in the same laboratory of Dr. Rudolph Juliano at the University of North Carolina, Department of Pharmacology. No speculation about the teaching of Yoo et al. is required; when the same lab substituted siRNA for antisense in the delivery mixture experiments of Yoo et al., siRNA did not demonstrate predictable results which would have been expected if such a mixture were obvious in view of the teaching of Yoo et al.

Thus, because of the differential activities demonstrated, as well as the poor effects demonstrated using siRNA, Kang evidences that a substitution of an siRNA oligonucleotide for an antisense oligonucleotide in a delivery mixture comprising a delivery agent consisting of a generation 2 to 5 dendrimer mixed with a nucleic acid capable of mediating RNAi would neither be obvious, nor be expected to achieve predictable results.

Furthermore, Applicant points to the failure of success of experiments utilizing a generation 5 dendrimer as a delivery agent in Bielinska et al. As discussed above, while a generation 7 dendrimer delivery agent conferred effective delivery and antisense activity, similar experiments utilizing a generation 5 dendrimer as delivery agent were ineffective at conferring either delivery or antisense activity. See Bielinska et al., at page 2180, last paragraph and Figure 8.

The failure of Kang et al. and Bielinska et al. to demonstrate results which would be predicted if the use of a generation 5 dendrimer as a delivery agent in a delivery mixture with a nucleic acid were obvious supports non-obviousness of the use of a generation 5 dendrimer. Thus, the results of Kang et al. and Bielinska et al. demonstrate that one skilled in the art would not have a reasonable expectation of success in achieving predictable results in view of the art. The Examiner seemingly discounts the lack of effective results demonstrated by Kang et al. as merely a single experiment under limited conditions and fails to give weight to the results. See Office Action at page 8, lower paragraph. The Examiner further emphasizes rather that there was a reasonable expectation of success of producing a delivery mixture. See Office Action at page 9, first two lines. Applicant respectfully disagrees with the conclusion stated in the Office Action and contends the lack of predictable results must be given proper consideration, as indicia of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18.

Applicant submits additional secondary considerations of non-obvious surprising results have also been demonstrated in the disclosure of the present application that further support the non-obviousness of the invention as claimed. Evidence of unexpected results can be used to rebut a *prima facie* case of obviousness. See, e.g., *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003). As discussed in the prior response, Applicant submits the delivery mixture comprising a delivery agent consisting of a generation 2 to 5 dendrimer mixed with a nucleic acid capable of mediating RNA interference as described and currently claimed confers delivery and efficacy which are far superior to those compositions described in Yoo et al. These levels would not be expected in view of the teaching of Yoo et al., whether alone or in combination with one or more of the additionally cited references.

The Examiner questions the results of the experiments, specifically, what generation dendrimer is used. Applicant has submitted in prior responses that a generation 4 dendrimer was used in the Experiments of the application as filed, and the (first) Rana Declaration was submitted in support of such assertions. As discussed above, Applicant submits herewith Rana Declaration 2 and attached Exhibits in further support of the fact that a generation 4 dendrimer was used in the experiments described in Examples 1, 2, and 7 of the instant application as filed and in Examples 2, 3, and 8 of the Priority Application as filed. See discussion above under the Rejection under 35 USC §112 for further details and discussion.

When a direct comparison of the experiments in the application as filed is made to those taught by Yoo et al., a delivery mixture comprising a delivery agent consisting of a generation 4 dendrimer mixed with an antisense nucleic acid did not confer activity. In contrast, the present application shows that a delivery mixture comprising a delivery agent consisting of a generation 4 dendrimer mixed with an siRNA nucleic acid yielded RNA inhibition comparable to the standard transfection agent LIPOFECTAMINE™. In view of the fact that no activity was demonstrated in Yoo et al., certainly the results generated in the Examples are new and unexpected in view of the teaching of Yoo et al.

In addition to unexpected results, delivery mixtures comprising a delivery agent consisting of a generation 2 to 5 dendrimer mixed with a nucleic acid capable of mediating RNAi have properties which are not possesed by prior delivery mixtures. Such properties are further supportive of non-obviousness of the claimed compositions, as the "presence of a property not possessed by the prior art is evidence of nonobviousness." *In re Papesch*, 315 F.2d 381, (CCPA 1963). As discussed in Applicant's prior response, activity of the mixtures does not appear to correlate consistently with increased concentration of dendrimer. Rather, dendrimer concentrations below 20μg/mL or above 40μg/mL were found to be less effective in conferring efficient cell uptake and RNAi activity. See Examples 1 and 2, paragraphs 102-103, and Figures 1 and 2 of the application as published. Furthermore, Applicant has found cellular localization conferred by delivery mixtures is critical for efficient activity of the delivery mixtures and RNAi activity in the cell. For example, delivery mixtures comprising an effective amount of dendrimer localize siRNA to perinuclear regions of the cytoplasm as well as nuclear regions. Higher amounts of dendrimer mixtures, which were less efficient for delivery, appeared to disrupt cellular localization, indicating that subcellular localization of siRNA is important for RNAi activity. See Examples 6 and 7, paragraphs 110-111, and Figures 8 and 9 of the application as published.

Finally, delivery mixtures comprising a delivery agent consisting of a generation 2 to 5 dendrimer mixed with a nucleic acid capable of mediating RNAi did not have toxic effects on cells as reported by Yoo et al. Such lack of toxicity is further support of non-obviousness of the instant invention, because "absence of property which a claimed invention would have been expected to possess based on the teachings of the prior art is evidence of unobviousness." *Ex parte Mead Johnson & Co.* 227 USPQ 78 (Bd. Pat. App. & Inter. 1985)

Thus, the delivery mixture comprising a delivery agent consisting of a generation 2 to 5 dendrimer mixed with a nucleic acid capable of mediating RNA interference disclosed and claimed in the present application provides superior properties to the delivery mixture described in Yoo et al. such that the presently claimed invention would not be obvious and taught by any of Woolf, Yoo et al., Olejnik et al., and Grigoriev et al., whether alone or in combination. Furthermore, provided delivery mixtures possess properties which differentiate the compositions from those of the prior art so as to render the

compositions non-obvious. Thus, even if a *prima facie* case of obviousness had been made, the unexpected superior results and properties demonstrated by Applicant are secondary considerations sufficient to rebut such a showing.

In view of the above, Applicant submits that the invention as provided and presently claimed would not be obvious to one skilled in the art; as such the rejection under 35 USC 103(a) should be withdrawn. Reconsideration and withdrawal of the rejection is respectfully requested.

Rejection under 35 USC § 103(a) over Yoo et al., in view of Hammond et al., Tuschl et al., and McManus et al.

Claims 14, 17-24 and 32-44 remain rejected under 35 USC §103(a) as being unpatentable over Yoo et al. in view of Hammond et al., Tuschl et al., and McManus et al.

Applicant appreciates the Examiner's acknowledgment that it would not be obvious to use a generation 4 dendrimer in view of the teaching of Yoo et al. Applicant reiterates traversal of the rejection maintained under 35 USC §103.

For all of the reasons discussed above, when considered as a whole, one skilled in the art would not arrive at the conclusion that Yoo et al. provides sufficient teaching such that one would expect that replacing the antisense molecule with a dsRNA (or any other nucleic acid capable of mediating RNA interference) would be effective for mediating RNA interference. Given the knowledge in the field at the time of the invention, one skilled in the art would not consider such a combination to be obvious, as it was not known or expected that such a replacement would yield predictable results with a reasonable expectation of success.

Alone or in combination, Hammond et al., Tuschl et al., or McManus et al. do not remedy the deficiency of Yoo et al. When considered as a whole, the teachings of Yoo et al. in view of Hammond et al., Tuschl et al., and McManus et al., taken alone or in combination, can only suggest that one skilled in the art *try* to substitute any of a dsRNA, siRNA, shRNA or microRNA for antisense in a delivery mixture of Yoo et al. Neither Hammond et al., Tuschl et al., or McManus et al., considered alone or in combination with Yoo et al., remedy the deficiencies of Yoo et al.. A mere suggestion to experiment is not the standard supportive of an obviousness rejection under 35 USC § 103.

As discussed above in the previous section addressing rejections under 35 USC § 103, secondary considerations have been presented which support a rebuttal of obviousness, were it concluded that a *prima facie* case of obviousness has indeed been established, which Applicant traverses.

As discussed above, when the replacement proposed by the Examiner (i.e., replacement of an antisense oligonucleotide with an siRNA) was carried out in the same laboratory as the experiments and results described in Yoo et al., the results using siRNA were not as good as the results demonstrated using antisense. See Kang et al. Furthermore, the failure of Bielinska et al. to demonstrate effective antisense delivery using a generation 5 dendrimer further supports a lack of reasonable expectation of success of use of a generation 5 dendrimer in delivery mixtures. Failure of others is one of the secondary considerations or indicia of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966). Thus, the failed results of Kang et al. utilizing a delivery mixture comprising a delivery agent consisting of a dendrimer mixed with an siRNA -- and the failed results of Bielinska et al. utilizing a delivery mixture comprising a delivery agent consisting of a generation 5 dendrimer mixed with an antisense nucleic acid -- support a conclusion of non-obviousness of a delivery mixture comprising a delivery agent consisting of a generation 2 to 5 dendrimer mixed with a nucleic acid capable of mediating RNA interference.

Moreover, Applicant's showing of evidence of unexpected results can be used for rebuttal if a *prima facie* case of obviousness were presented. See secondary considerations and evidence of unexpected superior results discussed *supra*. For the same reasons as discussed above, the delivery mixture comprising a delivery agent consisting of a generation 2 to generation 5 dendrimer mixed with a nucleic acid capable of mediating RNA interference as described and currently claimed confers delivery and efficacy *which are far superior* to those compositions described in Yoo et al., and would therefore be considered non-obvious.

In sum, Applicant submits that the invention as claimed would not have been obvious to one skilled in the art at the effective filing date because:

(1) When the art is considered as a whole, a generation 5 dendrimer would not be selected as a preferred delivery agent because the art teaches:

a) generation 5 dendrimers are not the optimal generation dendrimers for use, and

b) a lack of demonstrated activity of a generation 5 dendrimer teaches away from the use of a generation 5 dendrimer as a preferred delivery agent;

(2) Numerous optimization parameters necessary for modification of a delivery mixture, which amounts to infinite conditions such that one skilled in the art would not have a reasonable expectation of success in providing a delivery mixture according to the presently claimed invention using only routine experimentation; and

(3) Even assuming a *prima facie* case of obviousness has been made, which Applicant traverses, secondary considerations are sufficient to rebut such a *prima facie* case of obviousness based on:

a) the failure of others to demonstrate predictable results have been shown:

i. Bielinska et al. failed to achieve predictable results using a delivery mixture comprising a generation 5 dendrimer and antisense. Bielinska et al. failed to demonstrate transfection activity of antisense using a delivery mixture comprising a generation 5 dendrimer.

ii. Kang et al. failed to achieve predictable results using a delivery mixture comprising a delivery agent consisting of a generation 5 dendrimer mixed with a nucleic acid capable of mediating RNAi. Side-by side experiments with antisense and siRNA demonstrated that siRNA was only poorly effective compared to antisense.

b) Applicant's own experiments, which demonstrate non-obvious, surprising results because there was no reasonable expectation that making changes to a delivery mixture comprising a delivery agent consisting of a generation 2 to 5 dendrimer mixed with a nucleic acid capable of mediating RNAi would lead to delivery *far improved over the prior art*, much less that such a delivery mixture would achieve results similar to that achieved by the industry standard transfection agent LIPOFECTAMINE™.

c) the delivery mixtures provided and claimed in the instant application have *properties that are unexpected and non-obvious* in view of the teaching in the art:

i. The instant delivery mixtures confer unique subcellular localization patterns, which are critical for efficient activity of delivery mixture and RNAi activity in the cell. There was no reasonable expectation that the delivery mixtures would possess such desirable properties, particularly in light of nuclear localization and delivery of prior delivery mixtures comprising dendrimers and antisense.

ii. The instant delivery mixtures do not confer toxic effects of prior delivery mixtures comprising dendrimers. There was no reasonable expectation that the delivery mixtures would possess the desirable property of nontoxicity, particularly in view of prior delivery mixtures.

In view of the above, Applicant submits the present rejection is not proper. Applicant requests reconsideration and withdrawal of the rejection under 35 USC 103(a).

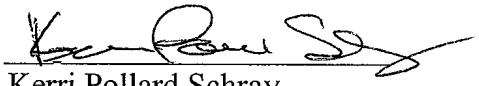
Entry and consideration of the amendments and remarks contained herein is respectfully requested. If at any time a telephone discussion would assist the Examiner and/or expedite prosecution, the Examiner is invited to contact the undersigned.

This paper is being filed timely as it is being filed with a petition for a one month extension of time, and the associated fees. It is believed that no additional fees and/or extensions of time are required. In the event that any additional extensions of time, fees and/or credits are necessary, the undersigned hereby authorizes the requisite fees to be charged and/or credited accordingly to Deposit Account No. 50-1582.

Respectfully submitted,

October 31, 2007

MIRICK, O'CONNELL, DEMALLIE & LOUGEE, LLP

By 

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